Year: 2018

Effectiveness of app-based self-acupressure for women with menstrual pain compared to usual care: A randomized pragmatic trial

Blödt, Susanne ; Pach, Daniel ; von Eisenhart-Rothe, Sanna ; Lotz, Fabian ; Roll, Stephanie ; Icke, Katja ; Witt, Claudia M

Abstract: BACKGROUND: Primary dysmenorrhea is common among women of reproductive age. Non-steroidal anti-inflammatory drugs and oral contraceptives are effective treatments, although the failure rate is around 20-25%. Therefore additional evidence-based treatments are needed. In recent years, the use of smartphone applications (apps) has increased rapidly and may support individuals in self-management strategies. OBJECTIVE: We aimed to investigate the effectiveness of app-based self-acupressure in women with menstrual pain. MATERIALS AND METHODS: A two-armed randomized pragmatic trial was conducted from December 2012 to April 2015 with recruitment until August 2014 in Berlin, Germany, among women aged 18-34 years with self reported cramping pain 6 on a numeric rating scale (NRS) for the worst pain intensity during the previous menstruation. After randomization women performed either app-based self-acupressure (n=111) or followed usual care only (n=110) for six consecutive menstruation cycles. The primary outcome was the mean pain intensity (NRS 0-10) on the days with pain during the third menstruation. Secondary outcomes included worst pain intensity during menstruation, duration of pain, 50% responder rates (reduction of mean pain by at least 50%), medication intake, sick leave days and body efficacy expectation assessed at the 1(st), 2(nd), 3(rd), and 6(th) menstruation cycle. RESULTS: We included 221 women (mean age 24.0 (sd 3.6) years). The mean pain intensity difference during the third menstruation was statistically significant in favor for acupressure (acupressure: 4.4 95% CI [4.0; 4.7]; usual care 5.0 [4.6; 5.3]; mean difference -0.6 [-1.2; -0.1], p=0.026). At the sixth cycle, the mean difference between the groups -1.4 [-2.0; -0.8] (p<0.001) reached clinical relevance. At the third and sixth menstruation cycle, responder rate was 37% and 58% respectively in the acupressure group in contrast to 23% and 24% in the usual care group. Moreover, the worst pain intensity (group difference -0.6 [-1.2; -0.02] and -1.4 [-2.0; -0.7]), the number of days with pain (-0.4 [-0.9; -0.01] and -1.2 [-1.6; -0.7]) and the proportion of women with pain medication at the third and sixth menstruation cycle (odd ratio 0.5 [0.3; 0.9] and 0.3 [0.2; 0.5]) was lower in the acupressure group. At the third cycle hormonal contraceptive use was more common in the usual care group than in the acupressure group (odds ratio 0.5 [0.3;0.97]), but not statistically significant different at the sixth cycle (odds ratio 0.6 [0.3;1.1]). The number of sick leave days and body efficacy expectation (self-efficacy scale) did not differ between groups. On a scale from 0-6, mean satisfaction with the intervention at the third cycle was 3.7 (sd 1.3), recommendation of the intervention to others 4.3 (1.5), appropriateness of acupressure for menstrual pain 3.9 (1.4), and application of acupressure for other pain 4.3 (1.5). The intervention was safe and after the sixth cycle two third of the women (67.6%) still applied acupressure on all days with pain. CONCLUSION: Smartphone app delivered self-acupressure resulted in a reduction of menstrual pain compared to usual care only. Effects were increasing over time and adherence was good. Future trials should include comparisons to other active treatment options.

DOI: https://doi.org/10.1016/j.ajog.2017.11.570

Effectiveness of app-based self-acupressure for women with menstrual pain compared to usual care: A randomized pragmatic trial

Susanne Blödt, Dipl. Biol., MScPH, Daniel Pach, MD, Dr. med., Sanna von Eisenhart-Rothe, Ms., MD, Fabian Lotz, Dipl.-Stat., Stephanie Roll, Dipl.-Stat., Dr. rer. med., Katja Icke, Mrs., Claudia M. Witt, Dr. med., MD, MBA

PII: S0002-9378(17)32335-9

DOI: 10.1016/j.ajog.2017.11.570

Reference: YMOB 11939

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 21 June 2017

Revised Date: 11 October 2017

Accepted Date: 9 November 2017

Please cite this article as: Blödt S, Pach D, Eisenhart-Rothe Sv, Lotz F, Roll S, Icke K, Witt CM, Effectiveness of app-based self-acupressure for women with menstrual pain compared to usual care: A randomized pragmatic trial, *American Journal of Obstetrics and Gynecology* (2017), doi: 10.1016/j.ajog.2017.11.570.

Effectiveness of app-based self-acupressure for women with menstrual pain compared to usual care: A randomized pragmatic trial

Susanne BLÖDT[1*], Dipl. Biol., MScPH; Daniel PACH, MD, Dr. med.[1*]; Sanna von EISENHART-ROTHE, Ms.[1], MD; Fabian LOTZ[1], Dipl.-Stat.; Stephanie ROLL[1], Dipl.-Stat., Dr. rer. med.; Katja ICKE, Mrs.[1], Claudia M WITT, Dr. med., MD, MBA[1,2,3]

[1]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Institute for Social Medicine, Epidemiology and Health Economics, 10117 Berlin, Germany

[2] Institute for Complementary and Integrative Medicine, University Zurich and University Hospital Zurich, 8091 Zurich, Switzerland

[3] University of Maryland School of Medicine, Center for Integrative Medicine, 520 W. Lombard Street, East Hall, Baltimore, MD 21201, USA

* Contributed equally

Corresponding Author:

Claudia Witt
Charité – Universitätsmedizin Berlin
Institute for Social Medicine, Epidemiology, and Health Economics
Luisenstr. 57
10117 Berlin
claudia.witt@charite.de

Tel: +49 30 450 529 011

Fax: +49 30 459 529 917

Disclosure statement: The authors report no conflict of interest.

Trial registration: at clinicaltrials.gov; Idenfication Number: NCT01582724.

Funding: This is an investigator initiated study that has not received any external funding.

Word count: 3283

Abstract: 497

Condensation sentence: Smartphone app delivered self-acupressure resulted in a reduction of menstrual pain compared to usual care only.

Short title: App-based treatment for menstrual pain

ABSTRACT

Background: Primary dysmenorrhea is common among women of reproductive age. Non-steroidal anti-inflammatory drugs and oral contraceptives are effective treatments, although the failure rate is around 20-25%. Therefore additional evidence-based treatments are needed. In recent years, the use of smartphone applications (apps) has increased rapidly and may support individuals in self-management strategies.

Objective: We aimed to investigate the effectiveness of app-based self-acupressure in women with menstrual pain.

Materials and Methods: A two-armed randomized pragmatic trial was conducted from December 2012 to April 2015 with recruitment until August 2014 in Berlin, Germany, among women aged 18-34 years with self reported cramping pain ≥6 on a numeric rating scale (NRS) for the worst pain intensity during the previous menstruation. After randomization women performed either app-based self-acupressure (n=111) or followed usual care only (n=110) for six consecutive menstruation cycles. The primary outcome was the mean pain intensity (NRS 0-10) on the days with pain during the third menstruation. Secondary outcomes included worst pain intensity during menstruation, duration of pain, 50% responder rates (reduction of mean pain by at least 50%), medication intake, sick leave days and body efficacy expectation assessed at the 1st, 2nd, 3rd, and 6th menstruation cycle.

Results: We included 221 women (mean age 24.0 (sd 3.6) years). The mean pain intensity difference during the third menstruation was statistically significant in favor for acupressure (acupressure: 4.4 95% CI [4.0; 4.7]; usual care 5.0 [4.6; 5.3]; mean difference −0.6 [−1.2; −0.1], p=0.026). At the sixth cycle, the mean difference between the groups −1.4 [−2.0; −0.8] (p<0.001) reached clinical relevance. At the third and sixth menstruation cycle, responder rate was 37% and 58% respectively in the acupressure group in contrast to 23% and 24% in the usual care group. Moreover, the worst pain intensity (group difference −0.6 [−1.2; −0.02] and −1.4 [−2.0; −0.7]), the number of days with pain (−0.4 [−0.9; −0.01] and −1.2 [−1.6; −0.7]) and the proportion of women with pain medication at the third and sixth menstruation cycle (odd ratio 0.5 [0.3; 0.9] and 0.3 [0.2; 0.5]) was lower in the acupressure group. At the third cycle hormonal contraceptive use was more common in the usual care group

than in the acupressure group (odds ratio 0.5 [0.3;0.97]), but not statistically significant different at the sixth cycle (odds ratio 0.6 [0.3;1.1]). The number of sick leave days and body efficacy expectation (self-efficacy scale) did not differ between groups.

On a scale from 0-6, mean satisfaction with the intervention at the third cycle was 3.7 (sd 1.3), recommendation of the intervention to others 4.3 (1.5), appropriateness of acupressure for menstrual pain 3.9 (1.4), and application of acupressure for other pain 4.3 (1.5). The intervention was safe and after the sixth cycle two third of the women (67.6%) still applied acupressure on all days with pain.

Conclusion: Smartphone app delivered self-acupressure resulted in a reduction of menstrual pain compared to usual care only. Effects were increasing over time and adherence was good. Future trials should include comparisons to other active treatment options.

Clinicaltrials.gov ID: NCT01582724

Keywords: acupressure, dysmenorrhea, mHealth, pain

INTRODUCTION

Primary dysmenorrhea[1] affects up to 81% of reproductive women,[2, 3] with approximately 15% suffering from severe pain.[2] Menstrual pain has a relevant impact on quality of life,[4] and results in a substantial economic loss.[5, 6]

Non-steroidal anti-inflammatory drugs and oral contraceptives are effective treatments,[7] although the failure rate is around 20-25%[5, 8, 9] due to side-effects[7, 10] and lack of effectiveness.[10-12] Additional evidence-based treatments are needed.[13] 70% of women with menstrual pain practice self-management.[10] A few studies have investigated the effect of self-acupressure for dysmenorrhea, mostly as an add-on to therapist-administered acupressure.[13-16] Although results showed a beneficial effect for self-acupressure,[17-21] the evidence is unclear due to risk of bias (mostly due to performance and attrition bias).[13]

In recent years, the use of smartphone applications (apps)[22] has increased rapidly. Mobile and electronic health solutions are already widely used in the general public and are seen as a valuable tool for various health problems[22-25] and self-management[26]. Mobile health (mHealth) solutions might have improved the autonomy and participation of users already,[26] for example by facilitating the search for information and health services, as well as by structuring of information and data. Health data is increasingly being collected via smartphones and portable devices (so-called wearables) and can be shared with doctors and other service providers. Individual behavior can be positively influenced with the help of behavioral change techniques and used, for example, for smoking cessation or weight control.[27, 28] Only few mHealth solutions have been investigated in randomized controlled trials to date and the majority of available apps do not report any health care professional involvement in their development[22, 25] Nevertheless, a strong increase in mHealth solutions and increasing integration into usual care is expected. App-based self-acupressure might be innovative to support women with menstrual pain, however up to now its effectiveness in a usual care setting is unclear.

We aimed to investigate whether app-based self-acupressure is more effective in reducing pain than usual care for women with menstrual pain.

MATERIALS AND METHODS

Design

We performed a two-armed, randomized pragmatic trial with a treatment duration and observation time of 6 menstruation cycles per woman. The design of the trial and the development of the smartphone app 'AKUD' were shaped by stakeholder engagement (see previous publication[29]). A statistician not involved in the study used 'ranuni' random number generator of the SAS/STAT software (version 9.2. SAS Inc., Cary, NC, USA) to generate the randomization list (1:1 ratio). The list was transferred into a secured database (Microsoft Office Access 2010® (Microsoft Corporation, Redmond, WA, USA)) and hidden behind the interface so that it was not accessible to anyone involved in the random allocation or treatment. Eligible women were randomized by clicking a button of the database interface. The result could not be changed, which ensured allocation concealment.

This study followed the standards of the Declaration of Helsinki [30] and the ICH-GCP guidelines, and was approved by the respective Ethics Committee (Charité – Universitätsmedizin Berlin EA1/027/12). All patients gave oral and written informed consent. The trial was registered at clinicaltrials.gov (NCT01582724) and the study protocol was published.[29]

Participants and Setting

Women were recruited in Berlin, Germany from December 2012 to August 2014, using information materials (posters, flyers, and leaflets), the intranet platforms of Charité – Universitätsmedizin Berlin, and students' email-lists. Additionally, the study was advertised on two Berlin subway lines for 5 months. Telephone interviews were used for participants' pre-screening. To facilitate recruitment, a financial compensation of 30 EUR was introduced after eight months.

Participants were eligible for the trial if they fulfilled the following inclusion criteria: female; 18-25 years of age (criterion broadened to 18-34 years after eight months of recruitment to facilitate recruitment); having dysmenorrhea defined as self-reported cramping pain during every menstrual cycle; no prior history of a gynecological disease that could be a reason for dysmenorrhea; having had menstruation in the last six weeks and a

duration of a menstruation cycle between 3 and 6 weeks; moderate or severe pain, defined as a score equal to or higher than 6 on a numeric rating scale (NRS, 0 to 10) for the worst pain intensity during the last menstruation; written and oral informed consent. Participants had to own a smartphone (iOS or Android) and to agree to enter study data through the app. Patients were not eligible for the trial if they fulfilled any of the following exclusion criteria: already using or planning to use: acupressure, acupuncture, shiatsu or/and tuina massage in the following 8 months; known pregnancy or planned pregnancy in the following 8 months.

Intervention and control group

Both treatment groups received the app AKUD (Software development: Smart Mobile Factory, Berlin, Germany), which included a visualization of the menstrual cycle, questionnaires and diaries for both groups.

Acupressure specific features were only available for the acupressure group. These included explanations of the acupressure procedure, drawings, videos, and photos of the acupressure points, as well as a timer to guide the one-minute acupressure of each point. The acupressure intervention (points, duration, setting) resulted from a written Delphi consensus with international acupuncture experts from China, Germany and the USA.[29] The acupuncture points SP6 (Sanyinjiao), LI4 (Hegu), and LR3 (Taichong) were used on both sides. In the acupressure group a health care professional introduced the acupressure based on the instruction of the app at the baseline visit (Table 1). The women were reminded by the app every noon to apply acupressure starting five days before the anticipated menstruation. User could switch off the reminders within the app. To keep the intervention standardized, the app received no major updates.

Women in the control group did not receive any study specific intervention. After the sixth menstruation cycle, i.e. end of the study, the acupressure features were activated within the app and a personal face-to-face introduction to acupressure was offered.

The acupressure and the control groups could continue with usual care during the study, which was defined as all medical and non-medical treatments with the exception of tuina, shiatsu, and acupuncture because of the use of similar pressure points.

Outcome measurements

The primary outcome measure was the mean pain intensity on the days with pain during the third menstruation on a numerical rating scale (NRS) from 0 (no pain) to 10 (worst possible pain) assessed retrospectively after the third menstruation.[31] The NRS and the time point were chosen based on the stakeholder process in preparation of the trial[29] and previous literature on acupressure on dysmenorrhea[14]. The NRS is easy to apply and well suited for implementation in a smartphone app and three months seem long enough to allow the development of an acupressure effect without risking recruitment or study adherence because of a relatively long study duration.

Secondary outcomes were assessed during and after the first, second, third, and sixth menstruation cycle by the app in both groups and included worst pain intensity during menstruation (NRS), duration of pain (number of days with pain), responder rates (50% reduction of mean pain intensity on the days with pain compared to the corresponding baseline value), pain medication, sick leave (days of absence from work or school due to menstrual pain), body efficacy expectation,[32] adverse events and suspected adverse reactions (intervention group only). Women in the acupressure group were also asked at the third cycle about satisfaction with the intervention. On the days where acupressure was recommended women were asked to record the number of acupressure sessions and the time they spent for the acupressure.

At baseline, self-reported data were collected by paper pencil. All other questionnaires and diaries were imbedded into the app. Most outcomes were collected by questionnaires within the app at the end of the menstruation, however data on pain medication and time spent for acupressure were collected by the app's diary. Women were reminded by app notifications every day at noon during the menstruation to fill in the questions of the diary. In addition they were reminded at the respective time point to complete the questionnaires at the last day of menstruation at the 1st, 2nd, 3rd, and 6th menstruation. In the acupressure group this notification was combined with the reminder to apply acupressure.

Statistical analysis

The study was designed to detect an effect size of 0.5 for the primary outcome measure (menstrual pain), with a power of 90% and a significance level of 5% using a two-sided t-test. Based on previous acupuncture studies, we assumed a mean of 5.5 in the control group and 4.0 in the intervention group, with a pooled standard deviation of 3 resulting in a total of 86 participants per group. Taking a potential drop-out rate of about 20% into account, 220 participants (110 per group) were planned. The primary analysis population was the full analysis set (FAS, with available data for the respective analysis) based on the intention-to-treat (ITT) principle of including each woman into the analysis according to her randomization group regardless of her adherence to the assigned intervention.

The primary analysis of the primary endpoint was an analysis of covariance (ANCOVA) with the treatment as fixed effect, the baseline NRS value as fixed covariate and a two-sided significance level of 5%. Secondary outcomes were analyzed similarly, i.e. ANCOVA, or logistic or Poisson regression (depending on the scale and distribution of the data), adjusted for the respective baseline value (if available).

As sensitivity analysis multiple imputation techniques were done using Markov Chain Monte Carlo approximation and FCS (fully conditional specification) methods.[33] The imputation model included all variables for the primary and secondary outcomes and age. Furthermore, in case of relevant differences in baseline variables between the treatment groups, those unbalanced variables were used as covariates for the analysis of the primary outcome. Additionally, we evaluated the subgroups of i) women with hormonal contraceptive use at baseline, ii) women with a migration background, and iii) age ≥ 26 vs. < 26 years. Subgroups were evaluated using the interaction term of the respective subgroup with the treatment group in the analysis model.

As further supportive analysis, mixed models for repeated measures (MMRM) was fitted to compare the treatment groups with respect to changes in the primary outcome over time. The model included terms for treatment (acupressure vs. control) and time as fixed main effects, an interaction term for treatment by time, the baseline value as covariate, and the subject as a random effect.

Analysis was done using SPSS 21.0 and SAS 9.4 (SPSS Inc., Chicago, USA).

RESULTS

Participants

The study was conducted between December 2012 and April 2015 with recruitment from December 2012 until August 2014.

Out of 446 screened women, 221 were eligible for the study and gave consent and were randomized either to self-acupressure (n=111) or to usual care (n=110)(Figure 1).

The women had a mean age of 24.0 (sd 3.6) years, were highly educated, with 89.6% having 12 or more years of school education (Table 2). 37 women (16.7%) had a migration background. At baseline, the mean pain intensity on the days with pain on the NRS was 6.2 (SD 1.6) and most women (81.0%) had taken medication during their last menstruation. The following group differences with possible relevance were seen at baseline: fewer women in the usual care group (65.1%) had a partner (acupressure group 78.4%) and more women in the usual care group used oral contraceptives (36.4% vs. 23.4%).

Outcomes

Both groups showed a reduction in pain at the third and sixth menstruation cycle. The primary outcome measurement (mean pain intensity on the days of pain during the third cycle after therapy start) showed a statistically significant difference in favor for the acupressure group (acupressure: 4.4 95% CI [4.0; 4.7]; usual care 5.0 [4.6; 5.3]; mean difference −0.6 [−1.2; −0.1], p=0.026; (Table 3 and Figure 2). At the sixth menstruation cycle, the mean difference between the groups increased (−1.4 95% CI [−2.0; −0.8], p<0.001) and was considered clinically relevant[34]. The effect size (Cohen's d) for the mean pain intensity was 0.24 at the third cycle and 0.63 at the sixth cycle. Moreover, the chance to be a responder was higher for women in the acupressure group after the first, the third, and the sixth cycle with odds ratios of 2.3 [1.0; 5.2], 2.0 [1.1; 3.6], and 4.4 [2.5; 7.9], respectively.

At the third and sixth menstruation cycle the worst pain intensity (group difference −0.6 [−1.2; −0.02] and −1.4 [−2.0; −0.7]), the

number of days with pain (−0.4 [−0.9; −0.01] and −1.2 [−1.6; −0.7]), and the proportion of women with pain medication (odd ratio 0.5 [0.3; 0.9] and 0.3 [0.2; 0.5]) was lower in the acupressure group. Hormonal contraceptive use was more common in the usual care group than in the acupressure group at the third cycle (odds ratio 0.5 [0.3;0.97]), but not statistically significant different at the sixth cycle (odds ratio 0.6 [0.3;1.1]). The number of sick leave days and body efficacy expectation (self-efficacy scale) did not differ between groups (Table 3).

On a scale from 0–6 mean satisfaction with the intervention at the third cycle was 3.7 (SD 1.3), recommendation of the intervention to others (4.3 (1.5)), appropriateness of acupressure for menstrual pain (3.9 (1.4)), and application of acupressure for other pain (4.3 (1.5)).

Findings were similar and no relevant difference between results of primary, sensitivity and subgroup analyses could be observed. The baseline characteristics of women in both groups, who dropped out before the third menstruation cycle, did not differ relevantly from those who did not drop out.

Safety data

In the self-acupressure group, 15 women reported having had at least one suspected adverse reaction (SAR). Over all cycles, the following SARs were mentioned: bruises (n=5), deterioration (n=3), pain in the hand (n=1), pressure pain (n=1), shift in menstruation cycle (n=3), dizziness (n=1), nausea (n=1), pain in the legs (n=1), tingling in a finger (n=2). Of those who mentioned a SAR, 10 women experienced a SAR at one cycle, 3 at 2 cycles, and 2 at 3 cycles. With the exception of one woman, all continued to apply self-acupressure. This woman stopped applying self-acupressure at the sixth cycle because of bruises, pressure pain, and tightness in the breast. She had already mentioned pressure pain at the first cycle, which had made it difficult to continue self-acupressure, though she did not state any SAR at the second and third cycles.

Two serious adverse events occurred in each treatment group (self-acupressure: hip surgery, hospitalization due to dizziness; usual care: surgery of the nose, appendix surgery). None was considered related to the trial or the trial intervention.

Adherence and practice time

Overall adherence was good, but declined slightly over time. At the first cycle, 108 (97.3%) of the women stated that they had practiced acupressure on at least one day during the menstruation cycle, and at the sixth cycle this number was 92 (82.9%). Fewer women practiced acupressure on all days with pain (first cycle 102 [91.9%]; second cycle 89 [80.1%]; third cycle 91 [82.0%]; sixth cycle 75 [67.6%]). The mean duration of one practice session was similar over all cycles (first cycle: before menstruation 5.3 minutes (mean) (SD 2.1), during menstruation 5.4 (1.7); sixth cycle: before menstruation 5.4 (1.5), during menstruation 5.3 (1.5), Table 3). Women spent about 82.5 minutes [95%CI: 73.2–91.7] for acupressure during the first cycle, and 78.8 minutes [68.8–88.8], 76.8 minutes [67.3–86.4], and 68.7 minutes [57.7–79.7] for the second, third and sixth cycle, respectively.

COMMENT

Participating women with menstrual pain who applied self-acupressure supported by a smartphone app experienced statistically significant different pain relief after three menstruation cycles in comparison to women who received usual care. After 6 menstruation cycles, in the intervention group pain further decreased, resulting in a clinically relevant difference between both groups.

The strengths of this trial include the randomized study design, the high number of participants for an interventional randomized trial on acupressure, and the high adherence and follow-up rates. By using a smartphone app for the delivery of the intervention and for data collection, the trial used a novel study approach. Moreover, we consider the results to be transferrable to standard care settings because this pragmatic trial resulted from an extensive stakeholder engagement process.[29]

However, the results of our trial might have been influenced by the selection of our sample. Although we aimed at a diverse sample by advertising on public transport almost ninety percent of participants had at least twelve years of school education which is more than the average population. Furthermore, one third of the screened women failed eligibility. These aspects do impact the generalizability of the results. Our outcome assessment was reduced to a minimum[29] because stakeholders suggested that the outcome assessment should be short and patient-relevant, and data should be collected by an app.

The whole trial duration, including the preparation for the app, took 4.5 years which is a long time for a trial on consumer technology.[35] In contrast, a longer follow-up time might have provided more insight about long-term use. Based on the development of the primary outcome over time a longer follow-up might have shown an even higher effect. However, due to the relatively short follow-up time it is also possible that we have over-estimated the impact of treatment. Recruitment for this trial was difficult, and a longer study duration might have had a further inhibiting impact on recruitment. For future studies, ways to accelerate recruitment are needed. To keep the intervention standardized, our app received no major updates. However, an advanced development of the app for future studies is already in progress.

Considering the large number of available mobile Health (mHealth) apps for smartphones, only few have been evaluated in an RCT setting.[27, 28, 36, 37] To our knowledge, no RCT evaluating a smartphone app using acupressure or targeting menstrual pain had previously been conducted. According to the updated Cochrane Review "Acupuncture for dysmenorrhoea," which included acupressure trials, evidence is insufficient to demonstrate whether or not acupuncture or acupressure are effective in treating primary dysmenorrhea due to the methodological limitation of the included studies.[13] Although our rigorously designed trial might support the evidence base in favor of acupressure, it might also be associated with a high risk of bias because of the lack of blinding.[38] However, we think that our trial can contribute valuable data to its effectiveness in usual care.

Our results might have practical implications, because they could add a self-care option to the recommended treatment options of oral contraceptives and non-steroidal anti-inflammatory medications, which are effective but have limitations due to side-effects[7, 10] and failure rates,[5] Moreover, self-care treatments such as rest, medication, heating pads, tea, exercise, and herbs are already practiced by women with menstrual pain.[10] Therefore an additional non-drug and self-care treatment option might fit well into women's perceptions of how to treat menstrual pain[39] and might further support self-empowerment of affected women.

In our trial, for self-care acupressure the effect increased over time showing clinical relevance on the pain scale after six cycles[34] and a responder rate of about 60%. A similar increase was also shown by a trial from Chen et al.[19] However, most trials on acupressure and dysmenorrhea had shorter follow-ups.[14] That the adherence was still high after three months and the effect increased over time is encouraging. Regarding the high prevalence of menstrual pain, a treatment option with a modest to moderate effect and a good safety profile might have a considerable public health impact and should be further evaluated. It would be interesting to compare app-based self-acupressure with other active treatment in future research.

To conclude, self-acupressure supported and evaluated by a smartphone app could achieve a sustainable reduction in pain and medication in comparison to usual care. This self-care intervention showed a high retention rate and was safe. We suggest that future

trials should provide long-term data and compare acupressure with other active treatments options among a more diverse target group.

LIST OF ABBREVIATIONS

CI=Confidence interval; FAS=Full analysis set; FCS=Fully conditional specification; ITT=Intention-to-treat; NRS=Numeric rating scale; SAR=Suspected adverse reaction

DECLARATIONS

Author contributions

D.P., S.B., S.R., C.M.W. and our stakeholder team conceived and designed the study. Data analysis were done by F.L. and data interpretation were done by F.L., S.R., S.B., D.P., S.E.R, K.I., and C.M.W. S.B. and D.P. wrote the first draft of the paper. All authors discussed the results, commented on the paper, and approved the final paper.

Acknowledgements

We thank Beatrice Eden and Iris Bartsch for app testing, and all patients for their participation in this study. We thank our stakeholder team.[29]

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

The app is not a commercial product. The authors do not have any financial stake in the success of the app. However, an advanced development of the app for future studies is already in progress.

Ethics approval

The Ethics Committee of the Charité – Universitätsmedizin Berlin approved the protocol of this study (approval no. EA1/027/12). All patients gave oral and written informed consent.

Transparency

SB, DP and CMW affirm that the study is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and any discrepancies from the study as planned have been explained.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because the patient's consent was not obtained for data sharing. However, the risk of identification is low, because the data are anonymized. Additional data are available on reasonable request from the corresponding author.

CONSENT FOR PUBLICATION

Not applicable

REFERENCES

1. COCO AS. Primary dysmenorrhea. AmFamPhysician 1999;60:489-96.
2. PITTS MK, FERRIS JA, SMITH AM, SHELLEY JM, RICHTERS J. Prevalence and correlates of three types of pelvic pain in a nationally representative sample of Australian women. The Medical journal of Australia 2008;189:138-43.
3. LATTHE P, LATTHE M, SAY L, GULMEZOGLU M, KHAN KS. WHO systematic review of prevalence of chronic pelvic pain: a neglected reproductive health morbidity. BMCPublic Health 2006;6:177.
4. IACOVIDES S, AVIDON I, BENTLEY A, BAKER FC. Reduced quality of life when experiencing menstrual pain in women with primary dysmenorrhea. Acta obstetricia et gynecologica Scandinavica 2014;93:213-7.
5. DAWOOD MY. Nonsteroidal anti-inflammatory drugs and changing attitudes toward dysmenorrhea. Am J Med 1988;84:23-9.
6. IACOVIDES S, AVIDON I, BAKER FC. What we know about primary dysmenorrhea today: a critical review. Hum Reprod Update 2015;21:762-78.
7. MARJORIBANKS J, PROCTOR M, FARQUHAR C, DERKS RS. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. Cochrane Database Syst Rev 2010:CD001751.
8. ZAHRADNIK HP, HANJALIC-BECK A, GROTH K. Nonsteroidal anti-inflammatory drugs and hormonal contraceptives for pain relief from dysmenorrhea: a review. Contraception 2010;81:185-96.
9. DAWOOD MY. Dysmenorrhea. ClinObstetGynecol 1990;33:168-78.
10. DE SANCTIS V, SOLIMAN A, BERNASCONI S, et al. Primary Dysmenorrhea in Adolescents: Prevalence, Impact and Recent Knowledge. Pediatric endocrinology reviews : PER 2015;13:512-20.
11. ORTIZ MI. Primary dysmenorrhea among Mexican university students: prevalence, impact and treatment. Eur J Obstet Gynecol Reprod Biol 2010;152:73-7.
12. CAMPBELL MA, MCGRATH PJ. Use of medication by adolescents for the management of menstrual discomfort. Archives of pediatrics & adolescent medicine 1997;151:905-13.
13. SMITH CA, ARMOUR M, ZHU X, LI X, LU ZY, SONG J. Acupuncture for dysmenorrhoea. Cochrane Database Syst Rev 2016;4:CD007854.
14. SMITH CA, ZHU X, HE L, SONG J. Acupuncture for primary dysmenorrhoea. Cochrane Database Syst Rev 2011:CD007854.
15. ABARAOGU UO, TABANSI-OCHUOGU CS. As Acupressure Decreases Pain, Acupuncture May Improve Some Aspects of Quality of Life for Women with Primary Dysmenorrhea: A Systematic Review with Meta-Analysis. Journal of acupuncture and meridian studies 2015;8:220-8.
16. KAFAEI ATRIAN M, ABBASZADEH F, SARVIEH M, SARAFRAZ N, ASGHARI JAFARABADI M. Investigating the effect of pressure on third liver point on primary dysmenorrhea: a randomized controlled clinical trial. Iranian Red Crescent medical journal 2013;15:848-53.
17. BAZARGANIPOUR F, LAMYIAN M, HESHMAT R, ABADI MA, TAGHAVI A. A randomized clinical trial of the efficacy of applying a simple acupressure protocol to the Taichong point in relieving dysmenorrhea. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2010;111:105-9.
18. WONG CL, LAI KY, TSE HM. Effects of SP6 acupressure on pain and menstrual distress in young women with dysmenorrhea. Complement Ther Clin Pract 2010;16:64-9.
19. CHEN HM, CHEN CH. Effects of acupressure at the Sanyinjiao point on primary dysmenorrhoea. Journal of advanced nursing 2004;48:380-7.
20. CHEN HM, CHEN CH. Effects of acupressure on menstrual distress in adolescent girls: a comparison between Hegu-Sanyinjiao matched points and Hegu, Zusanli single point. Journal of clinical nursing 2010;19:998-1007.
21. TAYLOR D, MIASKOWSKI C, KOHN J. A randomized clinical trial of the effectiveness of an acupressure device (relief brief) for managing symptoms of dysmenorrhea. J Altern Complement Med 2002;8:357-70.

22. LALLOO C, JIBB LA, RIVERA J, AGARWAL A, STINSON JN. "There's a Pain App for That": Review of Patient-targeted Smartphone Applications for Pain Management. Clin J Pain 2015;31:557-63.
23. STATISTA. Anzahl der Smartphone-Nutzer in Deutschland in den Jahren 2009 bis 2015 (in Millionen): Statista GmbH, 2016 (vol 2016).
24. RESEARCH2GUIDANCE. mHealth app Developer Economics 2015, 2015.
25. LUCHT M, BREDENKAMP R, BOEKER M, KRAMER U. Gesundheits-und Versorgungs-Apps. In: Freiburg S, ed. Freiburg, 2013.
26. KRAMER U, LUCHT M. Gesundheits- und Versorgungs-Apps: Hintergründe zu deren Entwicklung und Einsatz: Universitätsklinikum Freiburg, 2015.
27. WHITTAKER R, MCROBBIE H, BULLEN C, RODGERS A, GU Y. Mobile phone-based interventions for smoking cessation. Cochrane Database Syst Rev 2016;4:Cd006611.
28. FLORES MATEO G, GRANADO-FONT E, FERRE-GRAU C, MONTANA-CARRERAS X. Mobile Phone Apps to Promote Weight Loss and Increase Physical Activity: A Systematic Review and Meta-Analysis. J Med Internet Res 2015;17:e253.
29. BLÖDT S, SCHUTZLER L, HUANG W, et al. Effectiveness of additional self-care acupressure for women with menstrual pain compared to usual care alone: using stakeholder engagement to design a pragmatic randomized trial and study protocol. Trials 2013;14:99.
30. WM A. *Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.* Number of pages.
31. HUSKISSON E, SCOTT J. VAS Visuelle Analogskalen; auch VAPS Visual Analog Scales, NRS Numerische Rating Skalen; Mod. Kategorialskalen. *Handbuch psychosozialer Meßinstrumente - ein Kompendium für epidemiologische und klinische Forschung zu chronischer Krankheit*. Göttingen: Hofgrefe, 1993.
32. SCHÜTZLER L, WITT CM. Body-Efficacy Expectation: Assessment of Beliefs concerning Bodily Coping Capabilities with a Five-Item Scale. Evid Based Complement Alternat Med 2013;2013:152727.
33. VAN BUUREN S. Multiple imputation of discrete and continuous data by fully conditional specification. Statistical methods in medical research 2007;16:219-42.
34. KENDRICK DB, STROUT TD. The minimum clinically significant difference in patient-assigned numeric scores for pain. Am J Emerg Med 2005;23:828-32.
35. RILEY WT, GLASGOW RE, ETHEREDGE L, ABERNETHY AP. Rapid, responsive, relevant (R3) research: a call for a rapid learning health research enterprise. Clin Transl Med 2013;2:10.
36. MARCANO BELISARIO JS, HUCKVALE K, GREENFIELD G, CAR J, GUNN LH. Smartphone and tablet self management apps for asthma. Cochrane Database Syst Rev 2013;11:Cd010013.
37. FISHER E, LAW E, PALERMO TM, ECCLESTON C. Psychological therapies (remotely delivered) for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev 2015;3:Cd011118.
38. COLLABORATION TC. Chapter 8: Assessing risk of bias in included studies. In: Higgins J, Altman D, Sterne J, eds. *Cochrane Handbook for Systematic Reviews of Interventions*, 2011.
39. BLÖDT S, WITT C, HOLMBERG C. Women's reasons to participate in a clinical trial for menstrual pain – a qualitative study BMJ open 2016;13:e012592.

Figure Legend:

Figure 1. Trial flow chart
Figure 2. Mean pain intensity (unadjusted mean, 95% CI)

Table 1. Instructions for applying the acupressure

Carrying out acupressure Find a comfortable sitting position. The right point will feel more sensitive than the surrounding area, it can be that you feel a slight soreness. When you have found the point, massage the area with the thumb using medium force (strong enough, but not so strong that you injure yourself) in small circles. Pay attention that you use circular movements and do not rub back and forth. While massaging, you should notice a distinct sensation, e.g. slight soreness, tingling, hypersensitivity, or heaviness.
Method Concentrate on the points as you are massaging them. Massage the points on both sides consecutively for one minute each. Start the timer.
Application Begin 5 days before you get your period. As a function of the app, you will receive a reminder of when you should begin the acupressure. Before your period, carry out the acupressure twice a day if possible; on days when this is not possible, carry out the acupressure at least once a day. During your period, on the painful days carry out the acupressure at least twice a day. If you like, you can repeat the acupressure up to 5 times.

Table 2: Baseline Demographic and Clinical Characteristics of Trial Groups

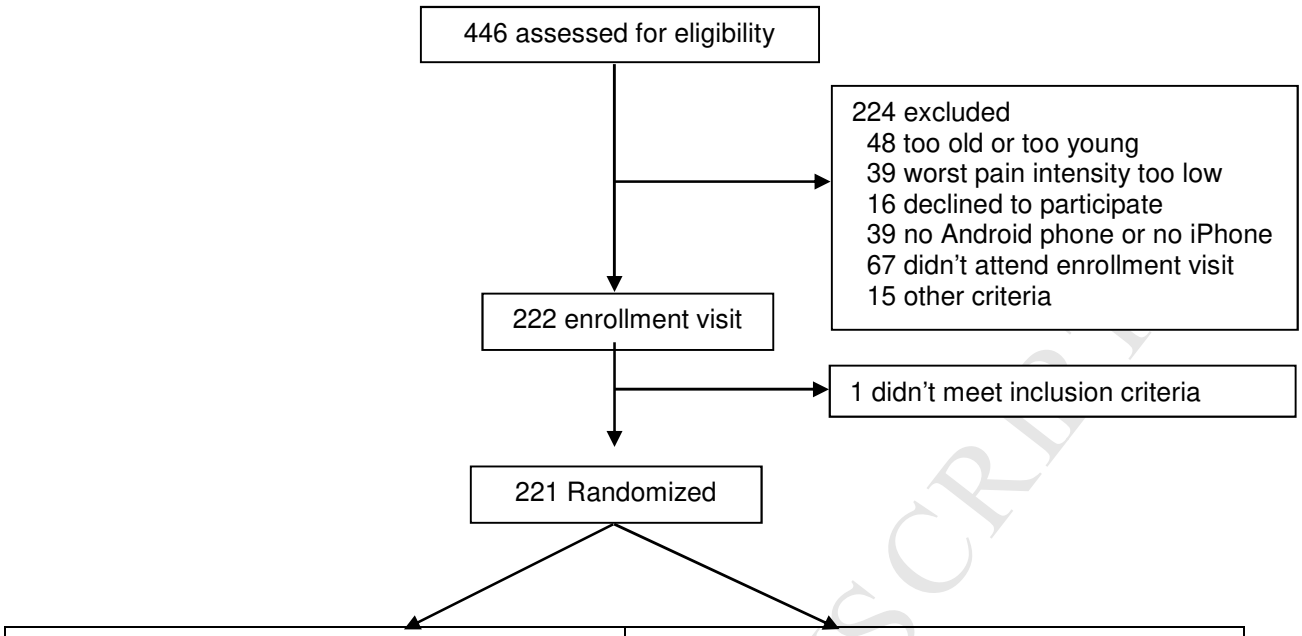
Characteristics	acupressure (n=111) mean±sd / n (%)	Usual care (n=110) mean±sd / n (%)
Age (years)	24.4±3.3	23.7±3.9
BMI (kg/m²)	22.0±3.8	21.8±3.1
≥ 12 years of school	98 (88.3)	100 (90.9)
Size of household		
single-person	17 (15.3)	20 (18.2)
multi-person	94 (84.7)	90 (81.8)
Partnership	87 (78.4)	71 (65.1)
Migrant background [38]§	20 (18.0)	17 (15.5)
Smartphone operating system		
iOS	45 (40.5)	38 (34.5)
Android	65 (58.6)	71 (64.5)
Duration of cycle (days)	28.7±2.7	28.7±2.5
Duration of menstruation (days)	5.4±1.4	5.2±1.0
Concomitant diseases	13 (11.7)	5 (4.5)
Complaints/pain*		
Abdominal cramps	98 (88.3)	88 (80.0)
Pain in lower abdomen	97 (87.4)	83 (75.5)
Back Pain	70 (63.1)	72 (65.5)
Headache	39 (35.1)	33 (30.0)
Nausea/vomiting	35 (31.5)	30 (27.3)
Other	31 (27.9)	40 (36.4)
Hormonal contraceptive	26 (23.4)	40 (36.4)
Sick leave days	0.6±0.7	0.5±0.7
Sport/Therapy against pain	41 (36.9)	48 (43.6)
Jogging	16 (14.4)	16 (14.5)
Fitness/gymnastics	13 (11.7)	20 (18.2)
Yoga	12 (10.8)	12 (10.9)
Meditation/relaxation	9 (8.1)	7 (6.4)
Dancing	2 (1.8)	8 (7.3)
Other	16 (14.4)	26 (23.6)
Mean pain (NRS 0-10)#	6.3±1.6	6.1±1.6
Worst pain (NRS 0-10)#	7.6±1.1	7.5±1.1
Number of days with pain	2.6±1.2	2.7±1.1
Pain medication intake	89 (80.2)	90 (81.8)
Body efficacy expectation	2.8±0.5	2.8±0.5

BMI=body mass index; NRS=numeric rating scale;
* multiple answers possible
#higher values=worst possible pain
§ Determination by assessment of primary language, place of birth and place of mother's and father's birth.

Table 3: Primary and secondary outcomes at first, second, third, and sixth menstruation cycle (adjusted for baseline value)

	Acupressure mean (95% CI) / proportion (95% CI)	Usual care mean (95% CI) / proportion (95% CI)	Differences acupressure vs. usual care mean (95% CI) / odds ratio (95% CI)	P value
Mean pain intensity during third menstruation cycle (NRS) [primary outcome]	4.4 (4.0; 4.7)	5.0 (4.6; 5.3)	-0.6 (-1.2; -0.1)	0.026
Mean pain intensity (NRS)				
First cycle	4.9 (4.5; 5.2)	5.2 (4.9; 5.5)	-0.3 (-0.8; 0.1)	0.171
Second cycle	4.6 (4.2; 5.0)	4.9 (4.5; 5.3)	-0.4 (-0.9; 0.2)	0.197
Sixth cycle	3.5 (3.1; 4.0)	5.0 (4.5; 5.4)	-1.4 (-2.0; -0.8)	<0.001
Worst pain intensity				
First cycle	6.2 (5.9; 6.6)	6.4 (6.1; 6.8)	-0.2 (-0.7; 0.3)	0.383
Second cycle	5.8 (5.4; 6.2)	6.1 (5.7; 6.5)	-0.3 (-0.8; 0.3)	0.374
Third cycle	5.6 (5.2; 6.0)	6.2 (5.8; 6.6)	-0.6 (-1.2; -0.02)	0.043
Sixth cycle	4.9 (4.4; 5.4)	6.3 (5.8; 6.8)	-1.4 (-2.0; -0.7)	<0.001
Number of days with pain				
First cycle	2.7 (2.4; 3.0)	2.8 (2.4; 3.1)	-0.05 (-0.5; 0.4)	0.828
Second cycle	2.3 (2.0; 2.6)	3.1 (2.8; 3.4)	-0.8 (-1.2; -0.3)	0.001
Third cycle	2.3 (2.0; 2.6)	2.7 (2.4; 3.0)	-0.4 (-0.9; -0.01)	0.047
Sixth cycle	1.9 (1.6; 2.2)	3.1 (2.7; 3.4)	-1.2 (-1.6; -0.7)	<0.001
Women with pain medication intake[a§]				
First cycle	0.5 (0.4; 0.6)	0.7 (0.6; 0.8)	0.4 (0.2; 0.8)	0.039
Second cycle	0.6 (0.5; 0.7)	0.7 (0.6; 0.8)	0.6 (0.3; 0.1)	0.051
Third cycle	0.6 (0.5; 0.7)	0.7 (0.6; 0.8)	0.5 (0.3; 0.9)	0.029
Sixth cycle	0.5 (0.4; 0.6)	0.8 (0.7; 0.8)	0.3 (0.2; 0.5)	<0.001
Number of days with pain medication				
First cycle	1.2 (1.0; 1.4)	1.4 (1.2; 1.6)	-0.2 (-0.6; 0.1)	0.110
Second cycle	1.1 (0.9; 1.3)	1.5 (1.3; 1.8)	-0.4 (-0.7; -0.1)	0.015
Third cycle	1.1 (0.9; 1.3)	1.5 (1.2; 1.7)	-0.4 (-0.7; -0.1)	0.021
Sixth cycle	0.9 (0.7; 1.0)	1.6 (1.4; 1.9)	-0.7 (-1.1; -0.4)	<0.001
Women with hormonal contraceptives [a§]				
First cycle	0.3 (0.2;0.3)	0.3 (0.3;0.4)	0.6 (0.3;1.1)	0.1155
Second cycle	0.2 (0.2;0.3)	0.3 (0.3;0.4)	0.6 (0.3;1.1)	0.0876
Third cycle	0.2 (0.2;0.3)	0.4 (0.3;0.5)	0.5 (0.3;0.97)	0.0399
Sixth cycle	0.2 (0.2;0.3)	0.4 (0.3;0.5)	0.6 (0.3;1.1)	0.0841
General change in menstrual pain*				
Third cycle	2.1 (1.9; 2.2)	2.8 (2.6; 2.9)	-	<0.001
Sixth cycle	1.8 (1.7; 2.0)	2.8 (2.7; 3.0)	-	<0.001
Responder rate[#a§]				
First cycle	0.2 (0.1; 0.3)	0.1 (0.05; 0.2)	2.3 (1.0; 5.2)	0.040
Second cycle	0.3 (0.2; 0.4)	0.2 (0.2; 0.3)	1.6 (0.9; 3.0)	0.109
Third cycle	0.4 (0.3; 0.5)	0.2 (0.2; 0.3)	2.0 (1.1; 3.6)	0.023
Sixth cycle	0.6 (0.5; 0.7)	0.2 (0.2; 0.3)	4.4 (2.5; 7.9)	<0.001
Sick leave days				
First cycle	0.3 (0.2; 0.4)	0.3 (0.2; 0.4)	0.04 (-0.1; 0.2)	0.497
Second cycle	0.2 (0.1; 0.3)	0.2 (0.1; 0.3)	0.01 (-0.1; 0.1)	0.854
Third cycle	0.3 (0.2; 0.4)	0.3 (0.2; 0.4)	-0.01 (-0.1; 0.1)	0.870
Sixth cycle	0.2 (0.1; 0.3)	0.2 (0.2; 0.3)	-0.1 (-0.2; 0.04)	0.250
Body efficacy expectation				
First cycle	2.8 (2.8; 2.9)	2.9 (2.8; 2.9)	-0.02(-0.1; 0.1)	0.629
Second cycle	2.8 (2.7; 2.9)	2.8 (2.7; 2.9)	0.02 (-0.1; 0.1)	0.698
Third cycle	2.9 (2.8; 3.0)	2.8 (2.7; 2.9)	0.1 (-0.04; 0.2)	0.195
Sixth cycle	2.9 (2.8; 3.0)	2.8 (2.7; 2.9)	0.05 (-0.1; 0.2)	0.424

NRS = numeric rating scale; * 1–5 scale (menstrual pain had: 1 = improved significantly, 2 = improved slightly, 3 = no change, 4 = worsened slightly, 5 = worsened significantly); # responder rate = mean pain reduced by at least 50%; § odds ratio; a proportion (95% CI)



111 Allocated to Acupressure	110 Allocated to Usual care
108 Follow-up at cycle 1 1 scheduling problems 1 pregnancy 1 no menstruation anymore	109 Follow-up at cycle 1 1 diagnosed with endometriosis
106 Follow-up at cycle 2 1 no smartphone anymore 1 without giving reasons	107 Follow-up at cycle 2 1 scheduling problems 1 pregnancy
102 Follow-up at cycle 3 2 no contact 1 no smartphone anymore 1 without giving reasons	107 Follow-up at cycle 3
95 Follow-up at cycle 6 2 no further interest 1 scheduling problems 1 lost contact 1 no menstruation anymore 1 pregnancy 1 without giving reasons	105 Follow-up at cycle 6 2 without giving reasons
102 used for primary endpoint analysis based on ITT*	107 used for primary endpoint analysis based on ITT

Allocation

Follow-Up

Primary Analysis

*ITT = Intention to treat

Figure 1. Trial flow chart

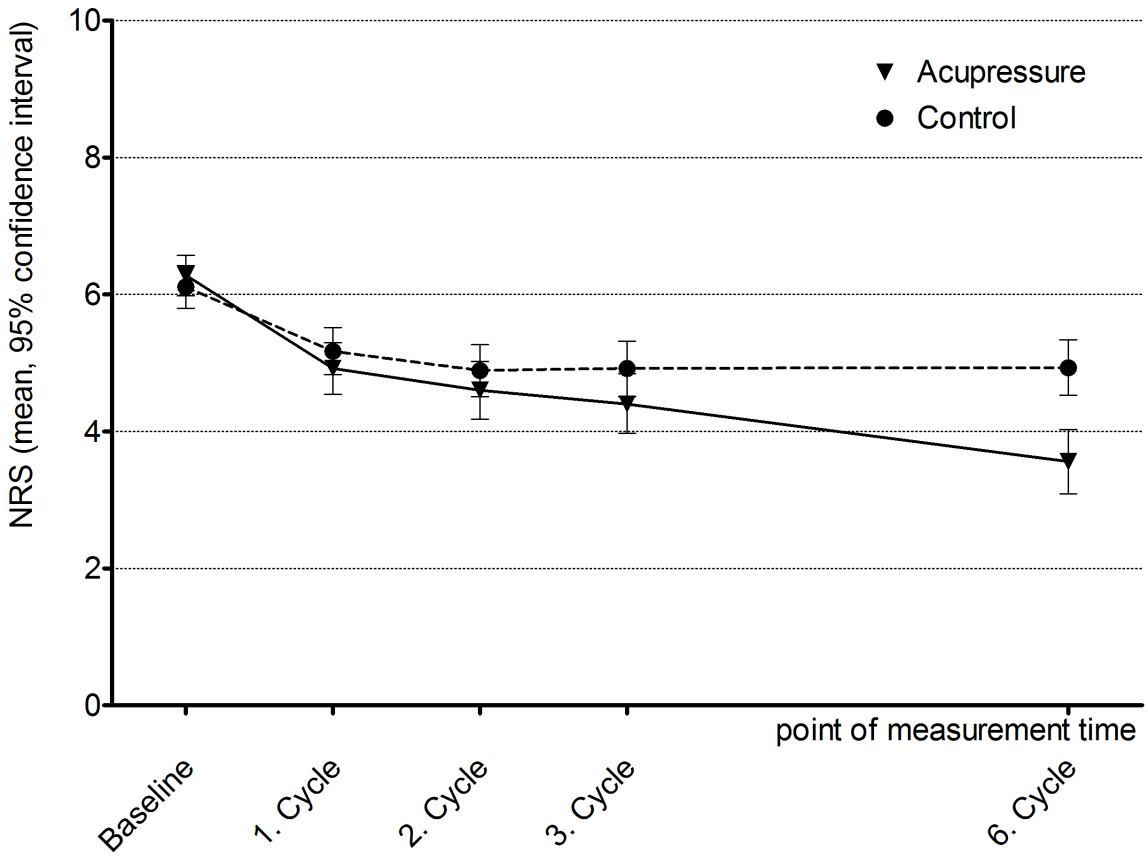


Figure 2. Mean pain intensity (unadjusted mean, 95% CI)